TITLE

Quinoline Derivatives as NK-2 and NK-3 Receptor Antagonists

FIELD OF THE INVENTION

The present invention relates to novel compounds, in particular to novel quinoline derivatives, to processes for the preparation of such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds in medicine.

BACKGROUND OF THE INVENTION

The mammalian peptide Neurokinin B (NKB) belongs to the Tachykinin (TK) peptide family which also include Substance P (SP) and Neurokinin A (NKA). Pharmacological and molecular biological evidence has shown the existence of three subtypes of TK receptor (NK_1, NK_2 and NK_3) and NKB binds preferentially to the NK_3 receptor although it also recognizes the other two receptors with lower affinity (Maggi et al, **1993**, *J. Auton. Pharmacol., 13*, 23-93).

Selective peptidic NK_3 receptor antagonists are known (Drapeau, **1990** *Regul. Pept.,* 31, 125-135), and findings with peptidic NK_3 receptor agonists suggest that NKB, by activating the NK_3 receptor, has a key role in the modulation of neural input in airways, skin, spinal cord and nigro-striatal pathways (Myers and Undem, 1993, *J.Physiol.*, 470, 665-679; Counture et al., 1993, *Regul. Peptides*, 46, 426-429; Mccarson and Krause, 1994, *J. Neurosci.*, 14 (2), 712-720; Arenas et al. 1991, *J.Neurosci.,* 11, 2332-8). However, the peptide-like nature of the known antagonists makes them likely to be too labile from a metabolic point of view to serve as practical therapeutic agents.

International Patent Application, Publication Number WO 00/58307 describes a series of aryl fused 2,4-disubstituted pyridines, such as naphthyridine derivatives, which are stated to exhibit biological activity as NK_3 receptor antagonists.

The compounds of the present invention are quinoline derivatives. Other quinoline derivatives have been described previously as selective NK_3 antagonists. For example, International Patent Application, Publication Numbers, WO 95/32948 and WO 96/02509 describe a series of selective and potent NK_3 receptor antagonists.

International Patent Application, Publication Number WO 00/64877 describes a series of 2-aminoquinolinecarboxamides as neurokinin receptor ligands.

International Patent Application, Publication Number, WO 00/58303 describes a series of 4-substituted quinoline derivatives which are stated to be NK_3 and/or GABA(A) receptor ligands. Such compounds are characterized by the presence of a nitrogen-containing heterocyclic moiety at the C(4) position of the quinoline ring.

International Patent Application, Publication Numbers, WO 97/21680, WO 98/52942, WO 00/31037, WO 00/31038, WO02/38547, WO 02/38548, WO 02/43734, WO 02/44154, and WO 02/44165 describe compounds which have biological activity as combined NK_3 and NK_2 receptor antagonists.

We have now discovered a further novel class of non-peptide NK_3 antagonists which are far more stable from a metabolic point of view than the known peptidic NK_3 receptor antagonists and are of potential therapeutic utility. These compounds also have NK_2 antagonist activity and are therefore considered to be of potential use in the prevention and treatment of a wide variety of clinical conditions, which are characterised by overstimulation of the Tachykinin receptors, in particular NK_3 and NK_2.

These conditions include respiratory diseases, such as chronic obstructive pulmonary disease (COPD), asthma, airway hyper-reactivity, cough; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis, rheumatoid arthritis and inflammatory pain; neurogenic inflammation or peripheral neuropathy, allergies such as eczema and rhinitis; ophthalmic diseases such as ocular inflammation, conjunctivitis, vernal conjuctivitis and the like; cutaneous diseases, skin disorders and itch, such as cutaneous wheal and flare, contact dermatitis, atopic dermatitis, urticaria and other eczematoid dermatitis; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systhemic lupus erythematosis; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease, irritable bowel syndrome (IBS), gastro-exophageous reflex disease (GERD); urinary incontinence and disorders of the bladder function; renal disorders; increased blood pressure, proteinuria, coagulopathy and peripheral and cerebral oedema following pre-eclampsia in pregnancies (hereinafter referred to as the 'Primary Conditions').

Certain of these compounds also show CNS activity and hence are considered to be of particular use in the treatment of disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as AIDS related dementia, senile dementia of the Alzheimer type, Alzheimer's disease, Down's syndrome, Huntingdon's disease, Parkinson's disease, movement disorders and convulsive disorders (for example epilepsy); demyelinating diseases such as multiple

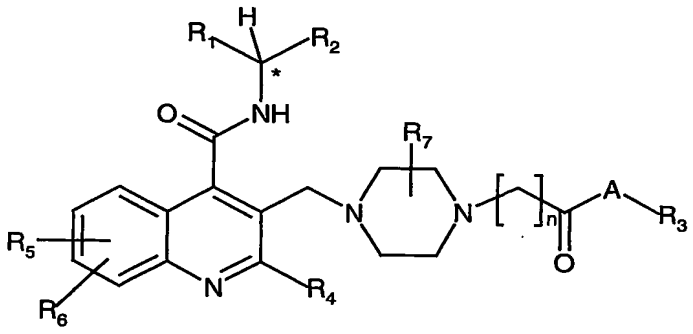
sclerosis and amyotrophic lateral sclerosis and other neuropathological disorders such as diabetic neuropathy, AIDS related neuropathy, chemotherapy-induced neuropathy and neuralgia; addiction disorders such as alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; eating disorders (such as food intake disease); fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of the blood flow caused by vasodilatation and vasospastic diseases such as angina, migraine and Reynaud's disease and pain or nociception, for example, that is attributable to or associated with any of the foregoing conditions especially the transmission of pain in migraine, (hereinafter referred to as the 'Secondary Conditions').

The compounds of formula (I) are also considered to be useful as diagnostic tools for assessing the degree to which neurokinin-3 and neurokinin-2 receptor activity (normal, overactivity or underactivity) is implicated in a patient's symptoms.

Certain compounds of the present invention have also been found to exhibit surprisingly advantageous pharmacochemical properties.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, there is provided a compound of formula (I) below or a pharmaceutically acceptable salt or solvate thereof:



(I)

wherein:

R_1 is H or substituted or unsubstituted (C_{1-6})alkyl;

R_2 is substituted or unsubstituted aryl, (C_{3-7})cycloalkyl, or heterocycle;

R_3 is H or substituted or unsubstituted (C_{1-6})alkyl, (C_{3-7})cycloalkyl, aryl or heterocycle;

A is NR_8 or O;

R_8 is H or substituted or unsubstituted (C_{1-6})alkyl;

R_4 is substituted or unsubstituted phenyl;

R_5 is H or up to three substitutents independently selected from the list consisting of alkyl, alkenyl, aryl, alkoxy, or a hydroxylated deriviative thereof, hydroxy, halogen, nitro, cyano, carboxy, alkylcarboxy, alkylcarboxyalkyl, haloalkyl, amino or mono- or dialkylamino; or R_5 represents a bridging moiety which is arranged to bridge two adjacent ring atoms wherein the bridging moiety comprises alkyl or dioxyalkylene;

R_6 is H or halo;

R_7 is oxo; and

n is 1 to 4.

Preferably, R_1 is methyl.

Suitably, R_2 is substituted or unsubstituted aryl or (C_{3-7})cycloalkyl. Preferably, R_2 is substituted or unsubstituted phenyl or cyclohexyl. Most preferably R_2 is unsubstituted cyclohexyl.

Preferably R_3 is (C_{1-6})alkyl or heterocycle. Methyl is a most perferred R_3 group. Other most preferred R_3 groups are substituted and unsubstituted morpholino, piperizine, pyrrole, pyrrolidine, piperidine, thiophene, imidazole, and pyrazole. Especially preferred groups are substituted and unsubstituted morpholino, piperizine, piperidine, and pyrrolidine.

Preferably R_8 is H or methyl.

Preferably R_4 is phenyl substituted with one to three fluorines. Most preferably R_4 is 3,5-difluorophenyl or 4-fluorophenyl.

Preferably R_5 is H or fluoro.

Preferably R_6 is H or fluoro.

Preferably n is 1.

Preferred compounds of formula (I) which are of special interest as agents useful in the treatment and/or prophylaxis of conditions which are characterised by overstimulation of the Tachykinin receptors, in particular NK_3 and NK_2, are:

2-(3,5-Difluoro-phenyl)-6-fluoro-3-{4-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-3-oxo-piperazin-1-ylmethyl}-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide;

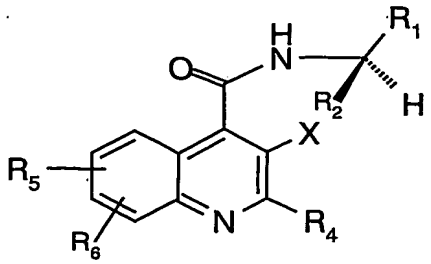
2-(3,5-Difluoro-phenyl)-6-fluoro-3-[3-oxo-piperidin-1-yl-ethyl)-piperazin-1-ylmethyl]-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide;

6-Fluoro-2-(4-fluoro-phenyl)-3-[4-(2-morpholin-4-yl-2-oxo-ethyl)-3-oxo-piperazin-1-ylmethyl]-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide;

6-Fluoro-2-(4-fluoro-phenyl)-3-{4-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-3-oxo-piperazin-1-ylmethyl}-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide; and

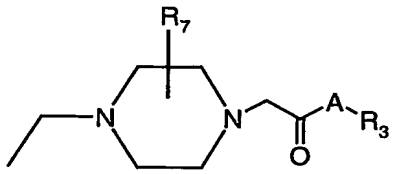
6-Fluoro-2-(4-fluoro-phenyl)-3-[3-oxo-4-(2-oxo-2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide; or a pharmaceutically acceptable salt thereof.

The compounds of formula (I) may have at least one asymmetric centre - for example the carbon atom labelled with an asterisk (*) in the compound of formula (I) - and therefore may exist in more than one stereoisomeric form. The invention extends to all such stereoisomeric forms and to mixtures thereof, including racemates. In particular, the invention includes compounds wherein the asterisked carbon atom in formula (I) has the stereochemistry shown in formula (Ib):



(Ib)

wherein R_1, R_2, R_4, R_5, and R_6 are as defined in relation to formula (I), and X represents the moiety



wherein R_7 and R_3 are as defined in relation to formula (I).

The compounds of formula (I) or their salts or solvates are preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, *inter alia*, having a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels.

A substantially pure form will generally contain at least 50% (excluding normal pharmaceutical additives), preferably 75%, more preferably 90% and still more preferably 95% of the compound of formula (I) or its salt or solvate.

One preferred pharmaceutically acceptable form is the crystalline form, including such form in pharmaceutical composition. In the case of salts and solvates the additional ionic and solvent moieties must also be non-toxic.

Suitable salts are pharmaceutically acceptable salts.

Suitable pharmaceutically acceptable salts include the acid addition salts with the conventional pharmaceutical acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric, succinic, benzoic, ascorbic and methanesulphonic.

Suitable pharmaceutically acceptable salts include salts of acidic moieties of the compounds of formula (I) when they are present, for example salts of carboxy groups or phenolic hydroxy groups.

Suitable salts of acidic moieties include metal salts, such as for example aluminium, alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for

example those with lower alkylamines such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine, quinine or quinoline.

Suitable solvates are pharmaceutically acceptable solvates.

Suitable pharmaceutically acceptable solvates include hydrates.

The term 'alkyl' or (C_{1-6})alkyl (unless specified to the contrary) when used alone or when forming part of other groups (such as the 'alkoxy' group) includes straight- or branched-chain alkyl groups containing 1 to 6 carbon atoms, examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert-butyl group.

The term 'alkenyl' or (C_{1-6})alkenyl (unless specified to the contrary) when used alone or when forming part of other groups includes straight- or branched- unsaturated carbon chains including at least one double C=C bond and containing 2-6 carbon atoms.

The term 'carbocylic' refers to cycloalkyl and aryl rings.

The term 'cycloalkyl' includes groups having 3 to 7 ring carbon atoms.

Suitable substituents for any (C_{1-6})alkyl, (C_{1-6})alkenyl, and (C_{3-7})cycloalkyl group include up to three substituents selected from the group consisting of hydroxy, halogen, nitro, cyano, carboxy, amino, mono- and di-(C_{1-6})alkylamino carboxamido, sulphonamido, (C_{1-6})alkoxycarbonyl, trifluromethyl, acyloxy, (C_{3-7})cycloalkyl, aryl, and heterocycle.

The term 'aryl' includes phenyl and naphthyl, preferably phenyl which unless specified to the contrary optionally comprise up to five, preferably up to three substituents selected from halogen, alkyl, phenyl, alkoxy, haloalkyl, hydroxyalkyl, hydroxy, amino, nitro, cyano, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, or alkylcarbonyl groups.

The term ' heterocycle' includes groups comprising aromatic heterocyclic rings containing from 5 to 12 ring atoms, suitably 5 or 6, and comprising up to four hetero-atoms in the or each ring selected from S, O or N.

Composite terms such as 'alkylcarboxy', 'cycloalkylalkyl' and so forth refer to components of a compound which include two interlinked groups, with the group named latterly in the term being the linking group, so that 'alkylcarboxy' means (alkyl)-COO- whilst 'cycloalkylalkyl' means (cycloalkyl)-(alkyl)-.

Unless specified to the contrary, suitable substituents for any heterocycle group includes up to 4 substituents selected from the group consisting of: alkyl, alkoxy, aryl and

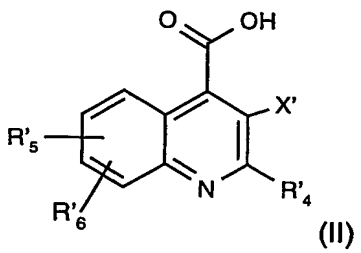
halogen or any two substituents on adjacent carbon atoms, together with the carbon atoms to which they are attached, may form an aryl group, preferably a benzene ring, and wherein the carbon atoms of the aryl group represented by the said two substituents may themselves be substituted or unsubstituted.

When used herein the term "halogen" refers to fluorine, chlorine, bromine and iodine, preferably fluorine, chlorine or bromine.

When used herein the term "acyl" includes residues of acids, in particular a residue of a carboxylic acid such as an alkyl- or aryl- carbonyl group.

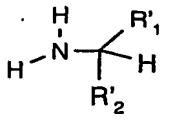
Certain reagents are abbreviated herein. DCC refers to dicyclohexylcarbodiimide, DMAP refers to dimethylaminopyridine, DIEA refers to diisopropylethyl amine, EDC refers to 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, hydrochloride. HOBt refers to 1-hydroxybenzotriazole, THF refers to tetrahydrofuran, DIEA refers to diisopropylethylamine, DEAD refers to diethyl azodicarboxylate, PPh_3 refers to triphenylphosphine, DIAD refers to diisopropyl azodicarboxylate, DME refers to dimethoxyethane, DMF refers to dimethylformamide, NBS refers to N-bromosuccinimide, Pd/C refers to a palladium on carbon catalyst, PPA refers to polyphosphoric acid, DPPA refers to diphenylphosphoryl azide, BOP refers to benzotriazol-1-yloxy-tris(dimethyl-amino)phosphonium hexafluorophosphate, HF refers to hydrofluoric acid, TEA refers to triethylamine, TFA refers to trifluoroacetic acid, PCC refers to pyridinium chlorochromate.

The invention also provides in one aspect a process for the preparation of a compound of formula (I), or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (II) or an active derivative thereof:



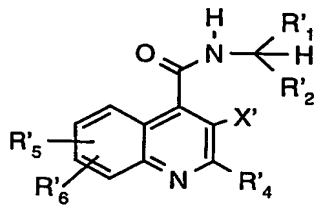
(II)

wherein R'_4, R'_5, R'_6 and X' are R_4, R_5, R_6 and X respectively as hereinbefore defined in relation to formula (I) or (Ib), or a group convertible to R_4, R_5, R_6 and X respectively; with a compound of formula (III):



(III)

wherein R'_1 and R'_2 are R_1 and R_2 as defined for formula (I) or a group or atom convertible to R_1 and R_2 respectively; to form a compound of formula (Ic):



(Ic)

wherein R'_1, R'_2, X', R'_4, R'_5 and R'_6 are as defined above, and thereafter carrying out one or more of the following optional steps:

(i) converting any one of R'_1, R'_2, X', R'_4, R'_5 and R'_6 to R_1, R_2, X, R_4, R_5 and R_6 respectively as required, to obtain a compound of formula (I);

(ii) converting a compound of formula (I) into another compound of formula (I); and

(iii) preparing a salt of the compound of formula (I) and/or a solvate thereof.

Suitable groups convertible into other groups include protected forms of said groups.

Suitably R'_1, R'_2, X', R'_4, R'_5 and R'_6 each represents R_1, R_2, X, R_4, R_5 and R_6 respectively or a protected form thereof.

It is favoured if the compound of formula (II) is present as an active derivative.

A suitable active derivative of a compound of formula (II) is a transient activated form of the compound of formula (II) or a derivative wherein the carboxy group of the compound of formula (II) has been replaced by a different group or atom, for example by an acyl halide, preferably a chloride, or an acylazide or a carboxylic acid anhydride.

Other suitable active derivatives include: a mixed anhydride formed between the carboxyl moiety of the compound of formula (II) and an alkyl chloroformate; an activated ester, such as a cyanomethyl ester, thiophenyl ester, p-nitrophenyl ester, p-nitrothiophenyl ester, 2,4,6-trichlorophenyl ester, pentachlorophenyl ester, pentafluorophenyl ester, N-hydroxy-phtalimido ester, N-hydroxypiperidine ester, N-hydroxysuccinimide ester, N-hydroxy benzotriazole ester; alternatively, the carboxy group of the compound of formula (II) may be activated using a carbodiimide or N,N'-carbonyldiimidazole.

The reaction between the compound of formula (II) or the active derivative thereof and the compound of formula (III) is carried out under the appropriate conventional

conditions for the particular compounds chosen. Generally, when the compound of formula (II) is present as an active derivative the reaction is carried out using the same solvent and conditions as used to prepare the active derivative, preferably the active derivative is prepared *in situ* prior to forming the compound of formula (Ic) and thereafter the compound of formula (I) or a salt thereof and/or a solvate thereof is prepared.

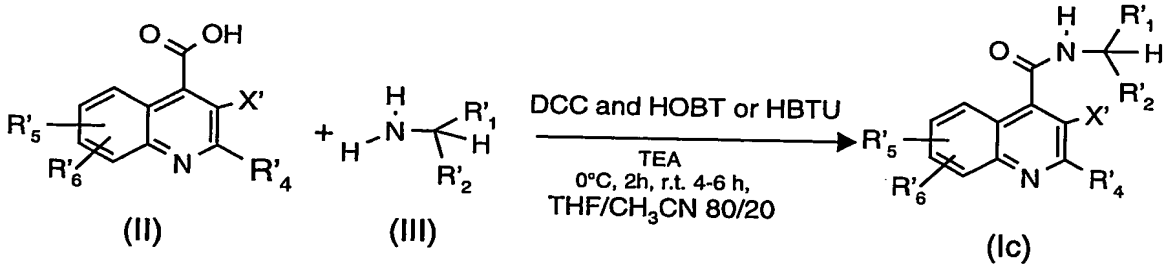
For example, the reaction between an active derivative of the compound of formula (II) and the compound of formula (III) may be carried out:

(a) by first preparing an acid chloride and then coupling said chloride with the compound of formula (III) in the presence of an inorganic or organic base in a suitable aprotic solvent such as dimethylformamide (DMF) at a temperature in a range from -70 to 50°C (preferably in a range from -10 to 20°C); or

(b) by treating the compound of formula (II) with a compound of formula (III) in the presence of a suitable condensing agent, such as for example N,N'-carbonyl diimidazole (CDI) or a carbodiimide such as dicyclohexylcarbodiimide (DCC) or N-dimethylaminopropyl-N'-ethylcarbodiimide, preferably in the presence of N-hydroxybenzotriazole (HOBT) to maximise yields and avoid racemization processes (see *Synthesis,* 453, 1972), or O-benzotriazol-1-yl-N,N,N',N'-tetramethyluroniumhexafluorophosphate (HBTU), in an aprotic solvent, such as a mixture of acetonitrile (MeCN) and tetrahydrofuran (THF), for example a mixture in a volume ratio of from 1:9 to 7:3 (MeCN:THF), at any temperature providing a suitable rate of formation of the required product, such as a temperature in the range of from -70 to 50°C, preferably in a range of from -10 to 25°C, for example at 0°C.

A preferred reaction is set out in Scheme 1 shown below:

Scheme 1



(II) (III) (Ic)

wherein R'_1, R'_2, X', R'_4, R'_5 and R'_6 are as defined above.

In the case in which the corresponding alkyl (such as methyl or ethyl) ester of compound (II) is utilised, an hydrolysis to compound (II) is required before conversion to

compound (Ic) in Scheme 1. Such hydrolysis can be carried out under acidic conditions, such 10-36% hydrochloric acid at a temperature in the range between 30 and 100 °C.

It will be appreciated that a compound of formula (Ic) may be converted to a compound of formula (I), or one compound of formula (I) may be converted to another compound of formula (I) by interconversion of suitable substituents. Thus, certain compounds of formula (I) and (Ic) are useful intermediates in forming other compounds of the present invention.

Accordingly, in a further aspect the invention provides a process for preparing a compound of formula (I), or a salt thereof and/or a solvate thereof, which process comprises converting a compound of the above defined formula (Ic) wherein at least one of R'_1, R'_2, X', R'_4, R'_5 and R'_6 is not R_1, R_2, X, R_4, R_5 or R_6 respectively, thereby to provide a compound of formula (I); and thereafter, as required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) into another compound of formula (I); and

(ii) preparing a salt of the compound of formula (I) and/or a solvate thereof.

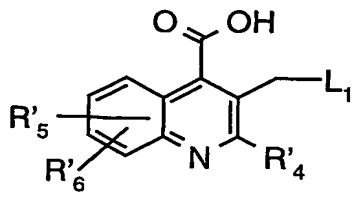
Suitably, in the compound of formula (Ic) the variables R'_1, R'_2, X', R'_4, R'_5 and R'_6 are R_1, R_2, X, R_4, R_5 and R_6 respectively or they are protected forms thereof.

The above mentioned conversions, protections and deprotections are carried out using the appropriate conventional reagents and conditions and are further discussed below.

A chiral compound of formula (III) wherein R_2 is a C_5 or C_7 cycloalkyl group, R_3 is methyl and R_1 is H are described in J. Org. Chem. (1996), 61 (12), 4130-4135. A chiral compound of formula (III) wherein R_2 is phenyl, R_3 is isopropyl and R_1 is H is a known compound described in for example Tetrahedron Lett. (1994), 35(22), 3745-6.

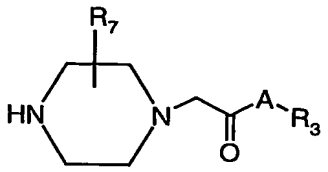
The compounds of formula (III) are known commercially available compounds or they can be prepared from known compounds by known methods, or methods analogous to those used to prepare known compounds, for example the methods described in Liebigs Ann. der Chemie, (1936), 523, 199.

In some embodiments of the invention, a compound of formula (II) or the corresponding alkyl (such as methyl or ethyl) ester is prepared by reacting a compound of formula (IV) or the corresponding alkyl (such as methyl or ethyl) ester:



(IV)

wherein R'_4, R'_5 and R'_6 are as defined above and L_1 represents a halogen atom such as a bromine atom, with a compound of formula (V):



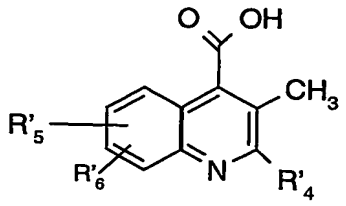
(V)

wherein R_3 and R_7 are as defined in relation to formula (I) or a protected form thereof.

Suitably, reaction between the compounds of formulae (IV) or the corresponding alkyl (such as methyl or ethyl) ester and (V) is carried out under conventional amination conditions, for example when L_1 is a bromine atom then the reaction is conveniently carried out in an aprotic solvent, such as tetrahydrofuran or dimethylformamide at any temperature providing a suitable rate of formation of the required product, usually at ambient temperature; preferably the reaction is carried out in the presence of triethylamine (TEA) or K_2CO_3.

The compounds of formula (V) are known, commercially available compounds or they can be prepared using methods analogous to those used to prepare known compounds; for example the methods described in the Chemistry of the Amino Group, Patais (Ed.), Interscience, New York 1968; Advanced Organic Chemistry, March J, John Wiley & Sons, New York, 1992 ; J. Heterocyclic Chem. (1990), 27, 1559; Synthesis (1975), 135, Bioorg. Med. Chem. Lett. (1997), 7, 555, or Protective Groups in Organic Synthesis (second edition), Wiley Interscience, (1991) or other methods mentioned herein.

A compound of formula (IV) or the corresponding alkyl (such as methyl or ethyl) ester may be prepared by appropriate halogenation of a compound of formula (VI) or the corresponding alkyl (such as methyl or ethyl) ester:



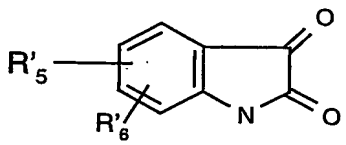
(VI)

wherein R'_4, R'_5 and R'_6 are as defined above in relation to formula (II).

Suitable halogenation reagents are conventional reagents depending upon the nature of the halogen atom required, for example when L_1 is bromine a preferred halogenation reagent is N-bromosuccinimide (NBS).

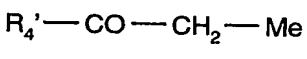
The halogenation of the compound of formula (VI) or the corresponding alkyl (such as methyl or ethyl) ester is suitably carried out under conventional conditions, for example bromination is carried out by treatment with NBS in an inert solvent, such as carbon tetrachloride CCl_4, or 1,2-dichloroethane or CH_3CN, at any temperature providing a suitable rate of formation of the required product, suitably at an elevated temperature such as a temperature in the range of 60°C to 100°C, for example 80°C; preferably the reaction is carried out in the presence of a catalytic amount of benzoyl peroxide.

A compound of formula (VI) is conveniently prepared by reacting a compound of formula (VII):



(VII)

wherein R'_5 and R'_6 are as defined in relation to formula (II), with a compound of formula (XIII):



(XIII)

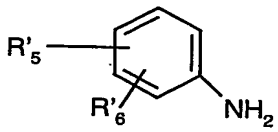
wherein R'_4 is as defined in relation to formula (II).

The reaction between the compounds of formula (VII) and (XIII) is conveniently carried out using Pfitzinger reaction conditions (see for example J. Prakt. Chem. 33, 100 (1886), J. Prakt. Chem. 38, 582 (1888), J. Chem. Soc. 106 (1948) and Chem. Rev. 35, 152 (1944)). For example in an alkanolic solvent such as ethanol, at any temperature providing a suitable rate of formation of the required product, but generally at an elevated temperature, such as the reflux temperature of the solvent, and preferably in the presence

of a base such as potassium hydroxide or potassium tert-butoxide. The Pfitzinger reaction may also be carried out in presence of an acid, such as acetic acid or hydrochloric acid, at a temperature providing a suitable rate of formation of the required product, but generally at an elevated temperature, as described in .J. Med. Chem. 38, 906 (1995).

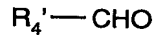
The compounds of formula (VII) are known compounds or they are prepared according to methods used to prepare known compounds for example those disclosed in J. Org. Chem. 21, 171 (1955); J. Org. Chem. 21, 169 (1955).

Alternatively a compound of formula (VI) may be conveniently prepared by reacting a compound of formula (XIV)



(XIV)

wherein R'_5 and R'_6 are as defined in relation to formula (II), with a compound of formula (XV):



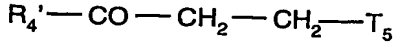
(XV)

wherein R'_4 is as defined in relation to formula (II) in presence of oxobutyric acid.

The reaction between the compounds of formula (XIV) and (XV) is conveniently carried out using Doebner reaction conditions (see for example Chem. Ber. 29, 352 (1894); Chem. Revs. 35, 153, (1944); J. Chem. Soc. B, 1969, 805), for example in an alcoholic solvent such as ethanol, at any temperature providing a suitable rate of formation of the required product, but generally at an elevated temperature, such as the reflux temperature of the solvent.

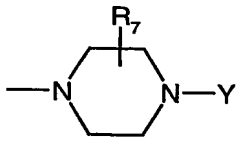
The compounds of formula (XIV) and (XV) are known compounds or they are prepared according to methods used to prepare known compounds for example as described in *Vogel's Textbook of Practical Organic Chemistry.*

In some alternative embodiments of the invention, a compound of formula (II) is prepared by reacting a compound of formula (VII) as defined above with a compound of formula (VIII):

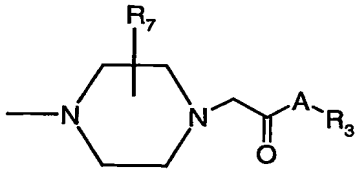


(VIII)

wherein R'_4 is as defined in relation to formula (II), and T_5 is a group

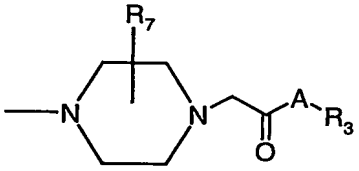


where Y is a protecting group such as a benzyl group, particularly a protecting group which is stable in basic conditions such as a terbutoxycarbonyl group; and thereafter as required removing any protecting group, for example by dehydrogenation, and/or converting any T_5 group to:



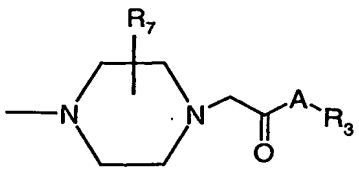
The reaction between the compounds of formula (VII) and (VIII) is conveniently carried out using Pfitzinger reaction conditions (see for example J. Prakt. Chem. 33, 100 (1886), J. Prakt. Chem. 38, 582 (1888), J. Chem. Soc. 106 (1948) and Chem. Rev. 35, 152 (1944)), for example in an alkanolic solvent such as ethanol, at any temperature providing a suitable rate of formation of the required product, but generally at an elevated temperature, such as the reflux temperature of the solvent, and preferably in the presence of a base such as potassium hydroxide or potassium tert-butoxide.

Protected forms of,



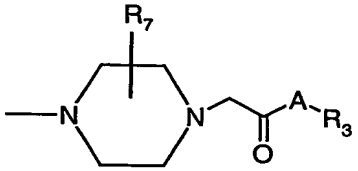
will vary according to the particular nature of the group being protected but will be chosen in accordance with normal chemical practice.

Groups convertible to,

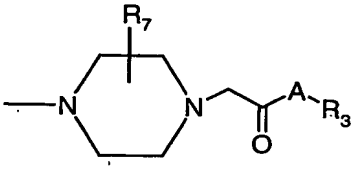


include groups dictated by conventional chemical practice to be required and to be appropriate, depending upon the specific nature of the group under consideration.

Suitable deprotection methods for deprotecting protected forms of



and conversion methods for converting T_5 to,



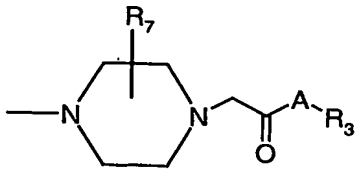
will be those used conventionally in the art depending upon the particular groups under consideration with reference to standard texts such as Greene, T.W. and Wuts, P.G.M. Protective Groups in Organic Synthesis, John Wiley & Sons Inc. New York, 1991 (Second Edt.) or in Kocienski, P.J. Protecting groups. George Thieme Verlag, New York, 1994 and Chemistry of the Amino Group, Patais (Ed.), Interscience, New York 1968; or Advanced Organic Chemistry, March J, John Wiley & Sons, New York, 1992.

A compound of formula (VIII) is prepared from a compound of formula (IX):

$$R_4'—CO—CH_2—CH_2—OH \qquad (IX)$$

wherein R'_5 is as defined in relation to formula (II), by first halogenating, preferably brominating, or mesylating the compound of formula (IX) and thereafter reacting the halogenation or mesylation product so formed with a compound capable of forming a group T_5 so as to provide the required compound of formula (VII).

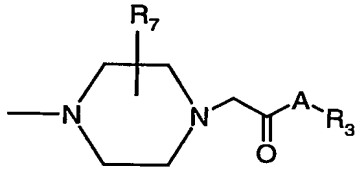
When T_5 is a group,



a compound capable of forming a group T_5 is a compound of the above defined formula (V).

The halogenation of the compound of formula (IX) is suitably carried out using a conventional halogenation reagent. Mesylation is conveniently carried out using mesyl chloride in an inert solvent such as methylene dichloride, at a temperature below room temperature, such as 0°C, preferably in the presence of triethylamine.

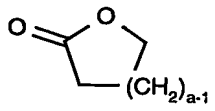
The reaction conditions between the compound of formula (IX) and the compound capable of forming a group T_5 will be those conventional conditions dictated by the specific nature of the reactants, for example when the T_5 required is a group,



and the required compound capable of forming a group T_5 is a compound of the above defined formula (V), then the reaction between the halogenation or mesylation product of the compound of formula (IX) and the compound of formula (V) is carried out under analogous conditions to those described for the reaction between the compounds of formulae (IV) and (V).

Other compounds capable of forming a group T_5 will depend upon the particular nature of T_5, but will be those appropriate compounds dictated by conventional chemical practice with reference to standard texts such as Chemistry of the Amino Group, Patais (Ed.), Interscience, New York 1968; and Advanced Organic Chemistry, March J, John Wiley & Sons, New York, 1992.

A compound of formula (IX) may be prepared by reacting a compound of formula (X):



(X)

wherein a is as defined in relation to formula (VIII), with a lithium salt of formula (XI):

$$R'_5\ Li \qquad (XI)$$

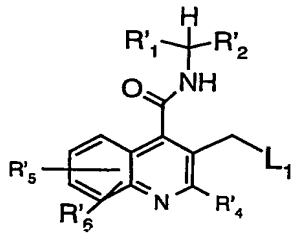
wherein R'_5 is as defined in relation to formula (II).

The reaction between the compounds of formulae (X) and (XI) can be carried out in an aprotic solvent, such as diethyl-ether at any temperature providing a suitable rate of formation of the required product, usually at a low temperature such as in the range of -10°C to -30°C, for example -20°C.

The compounds of formula (VII) are known compounds or they are prepared according to methods used to prepare known compounds for example those disclosed in J. Org. Chem. 21, 171 (1955); J. Org. Chem. 21, 169 (1955).

The compounds of formula (X) and (XI) are known compounds or they are prepared according to methods used to prepare known compounds for example those disclosed by Krow G. R. in Organic Reactions, Vol 43, page 251, John Wiley & Sons Inc.1994 (for the compounds of formula (X)) and Organometallics in Synthesis, Schlosser M.(Ed), John Wiley & Sons Inc.1994 (for the compounds of formula (XI)).

In another aspect, the present invention provides a process for the preparation of a compound of formula (I), or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (XVI):



(XVI)

wherein each of R'_1, R'_2, R'_4, R'_5, and R'_6 is respectively R_1, R_2, R_4, R_5, or R_6 as defined above or a group convertible to R_1, R_2, R_4, R_5, or R_6 respectively as defined above providing R'_2 is not aromatic in character, and L_1 represents a halogen atom such as a bromine atom, with a compound of formula (V) or a protected form thereof or a group convertible thereto; and thereafter carrying out one or more of the following optional steps:

(i) converting any one of R'_1, R'_2, R'_3, R'_4, R'_5, and R'_6 to R_1, R_2, R_3, R_4, R_5, and R_6 respectively as required, to obtain a compound of formula (I);

(ii) converting a compound of formula (I) into another compound of formula (I); and

(iii) preparing a salt of the compound of formula (I) and/or a solvate thereof.

Protected forms of compounds of formula (V) will vary according to the particular nature of the group being protected but will be chosen in accordance with normal chemical practice.

Groups convertible to R_3 include groups dictated by conventional chemical practice to be required and to be appropriate, depending upon the specific nature of the R_3 under consideration.

Suitable deprotection methods for deprotecting protected forms of R_3 and conversion methods for converting R'_3 to R_3 will be those used conventionally in the art depending upon the particular groups under consideration with reference to standard texts such as Greene, T.W. and Wuts, P.G.M. Protective Groups in Organic Synthesis, John Wiley & Sons Inc. New York, 1991 (Second Edt.) or in Kocienski, P.J. Protecting groups. George Thieme Verlag, New York, 1994 and Chemistry of the Amino Group, Patais (Ed.), Interscience, New York 1968; or Advanced Organic Chemistry, March J, John Wiley & Sons, New York, 1992.

Suitable groups convertible into other groups include protected forms of said groups.

Suitably R'_1, R'_2, R'_3, R'_4, R'_5, and R'_6 each represents R_1, R_2, R_3, R_4, R_5, and R_6 respectively or a protected form thereof.

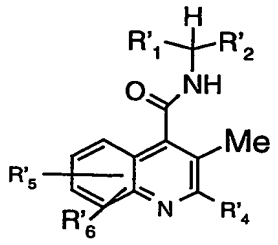
Suitable deprotection methods for deprotecting protected forms of R_1, R_2, R_3, R_4, R_5, and R_6 and conversion methods for converting R'_1, R'_2, R'_3, R'_4, R'_5, and R'_6 to R_1, R_2, R_3, R_4, R_5, and R_6 respectively will be those used conventionally in the art depending upon the particular groups under consideration with reference to standard texts such as Greene, T.W. and Wuts, P.G.M. Protective Groups in Organic Synthesis, John Wiley & Sons Inc. New York, 1991 (Second Edt.) or in Kocienski, P.J. Protecting groups. George Thieme Verlag, New York, 1994 and Chemistry of the Amino Group, Patais (Ed.), Interscience, New York 1968; or Advanced Organic Chemistry, March J, John Wiley & Sons, New York, 1992.

Suitably, reaction between the compounds of formulae (XVI) and (XVII) is carried out under conventional amination conditions, for example when L_1 is a bromine atom then the reaction is conveniently carried out in an aprotic solvent, such as tetrahydrofuran or dimethylformamide or acetonitrile at any temperature providing a suitable rate of formation of the required product, usually at ambient temperature; preferably the reaction is carried out in the presence of triethylamine (TEA), sodium hydride or K_2CO_3.

The compounds of formula (XVII) are known, commercially available compounds or they can be prepared using methods analogous to those used to prepare known compounds; for example the methods described in the Chemistry of the Amino Group,

Patais (Ed.), Interscience, New York 1968; Advanced Organic Chemistry, March J, John Wiley & Sons, New York, 1992 ; J. Heterocyclic Chem. (1990), 27, 1559; Synthesis (1975), 135, Bioorg. Med. Chem. Lett. (1997), 7, 555, or Protective Groups in Organic Synthesis (second edition), Wiley Interscience, (1991) or other methods mentioned herein.

A compound of formula (XVI) is prepared by appropriate halogenation of a compound of formula (XVIII):



(XVIII)

wherein R'_1, R'_2, R'_4, R'_5, and R'_6 are as defined above in relation to formula (XVI).

Suitable halogenation reagents are conventional reagents depending upon the nature of the halogen atom required, for example when L_1 is bromine a preferred halogenation reagent is N-bromosuccinimide (NBS).

The halogenation of the compound of formula (XVIII) is carried out under conventional conditions, for example bromination is carried out by treatment with NBS in an inert solvent, such as carbon tetrachloride CCl_4, or 1,2-dichloroethane or CH_3CN, at any temperature providing a suitable rate of formation of the required product, suitably at an elevated temperature such as a temperature in the range of 60°C to 100°C, for example 80°C; preferably the reaction is carried out in the presence of a catalytic amount of benzoyl peroxide.

Suitably, the compound of formula (XVIII) may be prepared by reacting a compound of formula (VI) as defined above or an active derivative thereof with a compound of formula (III) as defined above wherein R'_2 is not aromatic in character.

It is favoured if the compound of formula (VI) is present in the reaction mix as an active derivative, as hereinbefore described.

The reaction between the compound of formula (VI) or the active derivative thereof and the compound of formula (III) is carried out under the appropriate conventional conditions for the particular compounds chosen. Generally, when the compound of formula (VI) is present as an active derivative the reaction is carried out using the same

solvent and conditions as used to prepare the active derivative, preferably the active derivative is prepared *in situ* prior to forming the compound of formula (XVIII).

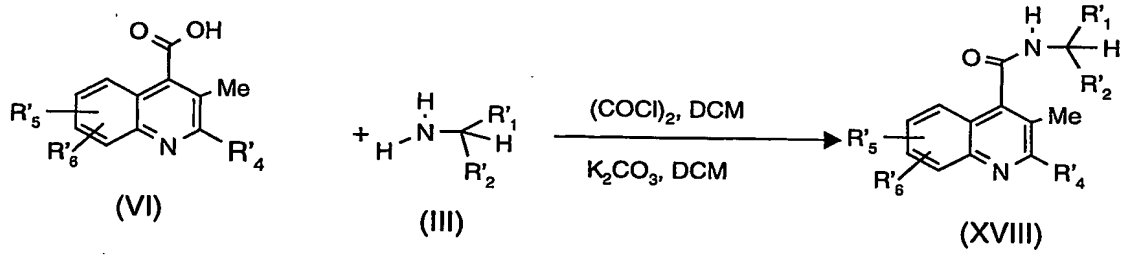
For example, the reaction between an active derivative of the compound of formula (VI) and the compound of formula (III) may be carried out:

(a) by first preparing an acid chloride and then coupling said chloride with the compound of formula (III) in the presence of an inorganic or organic base in a suitable aprotic solvent such as methylene dichloride or tetrahydrofuran at a temperature in a range from -70 to 50°C (preferably in a range from 20°C to reflux temperature); or

(b) by treating the compound of formula (VI) with a compound of formula (III) in the presence of a suitable condensing agent, such as for example N,N'-carbonyl diimidazole (CDI) or a carbodiimide such as dicyclohexylcarbodiimide (DCC) or N-dimethylaminopropyl-N'-ethylcarbodiimide, preferably in the presence of N-hydroxybenzotriazole (HOBT) to maximise yields and avoid racemization processes (see *Synthesis,* 453, 1972), or O-benzotriazol-1-yl-N,N,N',N'-tetramethyluroniumhexafluorophosphate (HBTU), in an aprotic solvent, such as a mixture of acetonitrile (MeCN) and tetrahydrofuran (THF), for example a mixture in a volume ratio of from 1:9 to 7:3 (MeCN:THF), at any temperature providing a suitable rate of formation of the required product, such as a temperature in the range of from -70 to 50°C, preferably in a range of from -10 to 25°C, for example at 0°C.

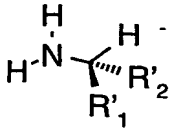
A preferred reaction is set out in Scheme 2 shown below:

Scheme 2

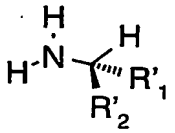


In the case in which the corresponding alkyl (such as methyl or ethyl) ester of compounds (VI) is utilised, a hydrolysis is required before conversion to compound (XVIII) in Scheme 2. Such hydrolysis can be carried out under acidic conditions, such 10-36% hydrochioric acid at a temperature in the range between 30 and 100 °C.

As hereinbefore mentioned, the compounds of formula (I) may exist in more than one stereoisomeric form - and the process of the invention may produce racemates as well as enantiomerically pure forms. Accordingly, a pure enantiomer of a compound of formula (I) can be obtained by reacting a compound of the above defined formula (II) with an appropriate enantiomerically pure primary amine of formula (IIIa) or (IIIc):

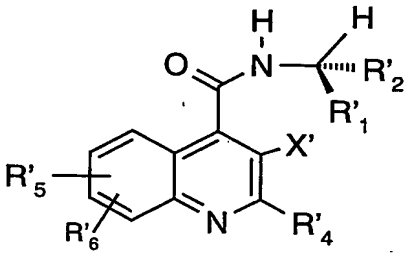


(IIIa)

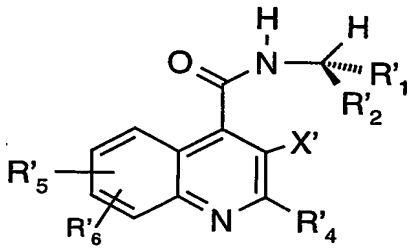


(IIIc)

wherein R'_1, and R'_2 are as defined above, to obtain a compound of formula (I'a) or (I'c):



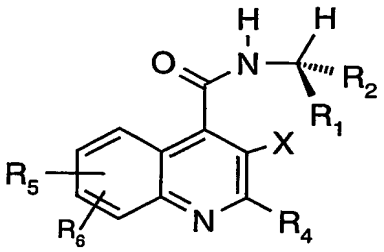
(I'a)



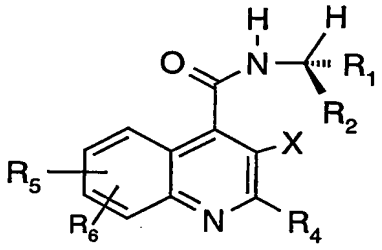
(I'c)

wherein R'_1, R'_2, X', R'_4, R'_5, and R'_6 are as defined above.

Compounds of formula (I'a) or (I'c) may subsequently be converted to compounds of formula (Ia) or (Ic) by the methods of conversion mentioned before:



(Ia)



(Ic)

wherein R_1, R_2, X, R_4, R_5, and R_6 are as defined above.

An alternative method for separating optical isomers is to use conventional, fractional separation methods in particular fractional crystallization methods. Thus, a pure enantiomer of a compound of formula (I) is obtained by fractional crystallisation of a

diastereomeric salt formed by reaction of the racemic compound of formula (I) with an optically active strong acid resolving agent, such as camphosulphonic acid, tartaric acid, O,O'-di-p-toluoyltartaric acid or mandelic acid, in an appropriate alcoholic solvent, such as ethanol or methanol, or in a ketonic solvent, such as acetone. The salt formation process should be conducted at a temperature between 20°C and 80°C, preferably at 50°C.

A suitable conversion of one compound of formula (I) into a further compound of formula (I) involves converting one group X into another group X by for example:

(i) converting a ketal into a ketone, by such as mild acidic hydrolysis, using for example dilute hydrochloric acid;

(ii) reducing a ketone to a hydroxy group by use of a borohydride reducing agent;

(iii) converting a carboxylic ester group into a carboxyl group using basic hydrolysis; and/or

(iv) reducing a carboxylic ester group to a hydroxymethyl group, by use of a borohydride reducing agent.

As indicated above, where necessary, the conversion of any group R'_1, R'_2, X', R'_4, R'_5, and R'_6 into R_1, R_2, X, R_4, R_5, and R_6 which as stated above are usually protected forms of R_1, R_2, X, R_4, R_5, or R_6 may be carried out using appropriate conventional conditions such as the appropriate deprotection procedure.

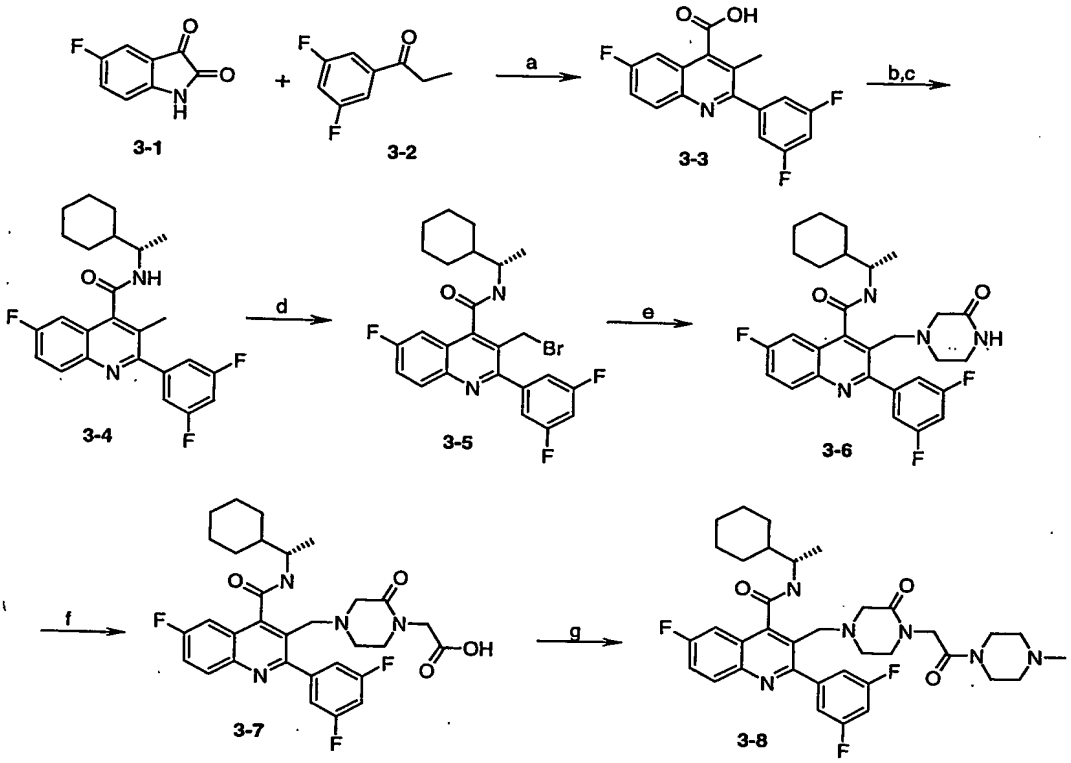
It will be appreciated that in any of the above mentioned reactions any reactive group in the substrate molecule may be protected and deprotected according to conventional chemical practice, for example as described by Greene, T.W. and Wuts, P.G.M. Protective Groups in Organic Synthesis, John Wiley & Sons Inc. New York, 1991 (Second Edt.) or in Kocienski, P.J. Protecting groups. George Thieme Verlag, New York, 1994.

Suitable protecting groups in any of the above mentioned reactions are those used conventionally in the art. Thus, for example suitable hydroxy protecting groups include benzyl or trialkylsilyl groups.

The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected. Thus for example a benzyloxy group may be prepared by treatment of the appropriate compound with a benzyl halide, such as benzyl bromide, and thereafter, if required, the benzyl group may be conveniently removed using catalytic hydrogenation or a mild ether cleavage reagent such as trimethylsilyl iodide or boron tribromide.

A preferred method of making the compounds of the present invention is illustrated in Scheme 3.

Scheme 3

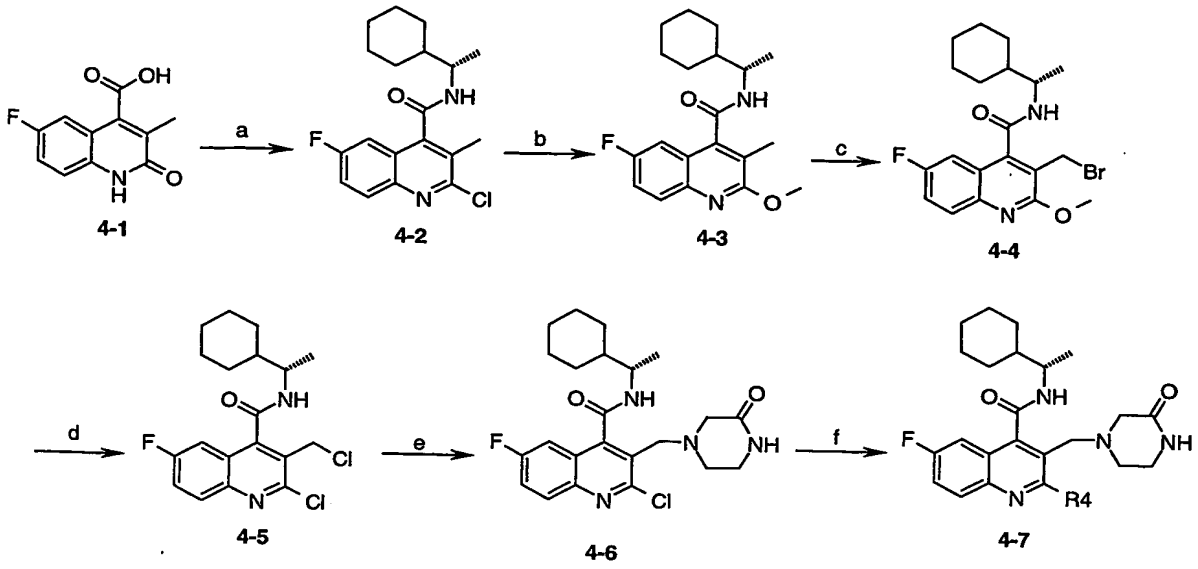


Reagents and Conditions: a) KOH, EtOH; b) Oxallyl chloride, DMF (cat.) CH_2Cl_2; c)(S)-Cyclohexylethylamine, triethylamine, CH_2Cl_2; d) NBS, dibenzoyl peroxide, CH_3CN; e) 2-oxo-piperazine, N,N-diisopropylethylamine; f) NaH, Iodoacetic acid ethylester, DMSO; g)1-methyl piperazine, HBTU, N,N-diisopropylethyl amine, DMF.

Thus, reaction of 5-fluoroisatin and 3,5-difluoropropiophenone under basic conditions produces carboxylic acid **3-3**. This is transformed to amide **3-4** via the acid chloride with subsequent reaction with (S)-cyclohexylethylamine. Bromination with NBS followed by S_N2 displacement of the bromide with 2-oxo-piperazine in the presence of Hunig's base produces compound **3-6**. Alkylation of the piperazinone nitrogen with iodoacetic acid ethylester in the presence of sodium hydride followed by hydrolysis under basic conditions provides acid **3-7**. Acid **3-7** may be converted to the desired amide under standard conditions using 1-methylpiperazine and HBTU in the presence of 4-methylmorpholine in DMF giving rise to amide **3-8.**

Alternatively, compounds depicted by **4-7** below (wherein R4 is as defined above), which corespond to compound **3-6** in Scheme 3 may be prepared *via* the method illustrated below in Scheme 4 Compound **4-7** can then be converted to a compound according to formula (I) by following the final two steps (f and g) of Scheme 3.

Scheme 4



Reagents and Conditions: a) oxallyl chloride, DMF (cat.) CH_2Cl_2; (S)-cyclohexylethylamine, triethylamine, CH_2Cl_2; b) CH_3OH, NaH; c) NBS, dibenzoyl peroxide, CH_3CN; d) oxallyl chloride, DMF (cat.) $CHCl_3$; e) 2-oxo-piperazine, N,N-diisopropylethylamine; f) $(R4)B(OH)_2$, Pd(0), dioxane-water.

Thus, treatment of acid **4-1** (for preparation, see Batt, D.G. et al. *Bioorg: Med. Chem. Lett.* **1998**, *8*, 1745) with oxalyl chloride completes two conversions: quinolinone to 2-chloro-quinoline and acid to acid chloride. The resultant acid chloride is reacted with (S)-1-cyclohexyl-ethylamine to afford the amide **4-2**. Reaction with methanol provides the 2-methoxy-quinoline **4-3**. Radical bromination with *N*-bromosuccinimide (NBS) followed by treatment with oxalyl chloride and displacement with 2-oxo-piperazine then furnishes **4-6**. Suzuki cross-coupling reaction with (R4)B(OH)2 affords the compound **4-7**.

As indicated above, the compounds of formula (I) have useful pharmaceutical properties.

Accordingly the present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance.

Accordingly the present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance.

In particular, the present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the treatment or prophylaxis of the Primary and Secondary Conditions.

The present invention further provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of the Primary and Secondary Conditions.

As mentioned abvove the Primary conditions include respiratory diseases, such as chronic obstructive pulmonary disease (COPD), asthma, airway hyperreactivity, cough; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis, rheumatoid arthritis and inflammatory pain; neurogenic inflammation or peripheral neuropathy, allergies such as eczema and rhinitis; ophthalmic diseases such as ocular inflammation, conjunctivitis, vernal conjuctivitis and the like; cutaneous diseases, skin disorders and itch, such as cutaneous wheal and flare, contact dermatitis, atopic dermatitis, urticaria and other eczematoid dermatitis; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systhemic lupus erythematosis; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease, irritable bowel syndrome (IBS), gastro-exophageous reflex disease (GERD); urinary incontinence and disorders of the bladder function; renal disorders.

As mentioned abvove,the Secondary conditions disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as AIDS related dementia, senile dementia of the Alzheimer type, Alzheimer's disease, Down's syndrome, Huntington's disease, Parkinson's disease, movement disorders and convulsive disorders (for example epilepsy); demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis and other neuropathological disorders such as diabetic neuropathy, AIDS related neuropathy, chemotherapy-induced neuropathy and neuralgia; addiction disorders such as alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; eating disorders (such as food intake disease); fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of the blood flow caused by vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease and pain or nociception, for example, that is attributable to or

associated with any of the foregoing conditions especially the transmission of pain in migraine.

Such a medicament, and a composition of this invention, may be prepared by admixture of a compound of the invention with an appropriate carrier. It may contain a diluent, binder, filler, disintegrant, flavouring agent, colouring agent, lubricant or preservative in conventional manner.

These conventional excipients may be employed for example as in the preparation of compositions of known agents for treating the conditions.

Preferably, a pharmaceutical composition of the invention is in unit dosage form and in a form adapted for use in the medical or veterinarial fields. For example, such preparations may be in a pack form accompanied by written or printed instructions for use as an agent in the treatment of the conditions.

The suitable dosage range for the compounds of the invention depends on the compound to be employed and on the condition of the patient. It will also depend, inter alia, upon the relation of potency to absorbability and the frequency and route of administration.

The compound or composition of the invention may be formulated for administration by any route, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may be designed to give slow release of the active ingredient.

Compositions may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

The compositions, for example those suitable for oral administration, may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinyl-pyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable setting agents such as sodium lauryl sulphate.

Solid compositions may be obtained by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. When the composition is in the form of a tablet, powder, or lozenge, any carrier suitable for

formulating solid pharmaceutical compositions may be used, examples being magnesium stearate, starch, glucose, lactose, sucrose, rice flour and chalk. Tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating. The composition may also be in the form of an ingestible capsule, for example of gelatin containing the compound, if desired with a carrier or other excipients.

Compositions for oral administration as liquids may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; aqueous or non-aqueous vehicles, which include edible oils, for example almond oil, fractionated coconut oil, oily esters, for example esters of glycerine, or propylene glycol, or ethyl alcohol, glycerine, water or normal saline; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

The compounds of this invention may also be administered by a non-oral route. In accordance with routine pharmaceutical procedure, the compositions may be formulated, for example for rectal administration as a suppository. They may also be formulated for presentation in an injectable form in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable liquid, e.g. sterile pyrogen-free water or a parenterally acceptable oil or a mixture of liquids. The liquid may contain bacteriostatic agents, anti-oxidants or other preservatives, buffers or solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such forms will be presented in unit dose form such as ampoules or disposable injection devices or in multi- dose forms such as a bottle from which the appropriate dose may be withdrawn or a solid form or concentrate which can be used to prepare an injectable formulation.

The compounds of this invention may also be administered by inhalation, via the nasal or oral routes. Such administration can be carried out with a spray formulation comprising a compound of the invention and a suitable carrier, optionally suspended in, for example, a hydrocarbon propellant.

Preferred spray formulations comprise micronised compound particles in combination with a surfactant, solvent or a dispersing agent to prevent the sedimentation of suspended particles. Preferably, the compound particle size is from about 2 to 10 microns.

A further mode of administration of the compounds of the invention comprises transdermal delivery utilising a skin-patch formulation. A preferred formulation comprises a compound of the invention dispersed in a pressure sensitive adhesive which adheres to the skin, thereby permitting the compound to diffuse from the adhesive through the skin for delivery to the patient. For a constant rate of percutaneous absorption, pressure sensitive adhesives known in the art such as natural rubber or silicone can be used.

As mentioned above, the effective dose of compound depends on the particular compound employed, the condition of the patient and on the frequency and route of administration. A unit dose will generally contain from 20 to 1000 mg and preferably will contain from 30 to 500 mg, in particular 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 mg. The composition may be administered once or more times a day for example 2, 3 or 4 times daily, and the total daily dose for a 70 kg adult will normally be in the range 100 to 3000 mg. Alternatively the unit dose will contain from 2 to 20 mg of active ingredient and be administered in multiples, if desired, to give the preceding daily dose.

No unacceptable toxicological effects are expected with compounds of the invention when administered in accordance with the invention.

The present invention also provides a method for the treatment and/or prophylaxis of the Primary and Secondary Conditions in mammals, particularly humans, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective, non-toxic pharmaceutically acceptable amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

The activity of the compounds of the present invention, as NK_3 ligands, is determined by their ability to inhibit the binding of the radiolabelled NK_3 ligands, [^{125}I]-[Me-Phe^7]-NKB or [^{3}H]-Senktide, to guinea-pig and human NK_3 receptors (Renzetti et al, **1991**, *Neuropeptide, 18*, 104-114; Buell et al, **1992**, *FEBS, 299(1)*, 90-95; Chung et al, **1994**, *Biochem. Biophys. Res. Commun., 198(3)*, 967-972).

The binding assays utilized allow the determination of the concentration of the individual compound required to reduce by 50% the [^{125}I]-[Me-Phe^7]-NKB and [^{3}H]-Senktide specific binding to NK_3 receptor in equilibrium conditions (IC50).

Binding assays provide for each compound tested a mean IC_{50} value of 2-5 separate experiments performed in duplicate or triplicate. The most potent compounds of the present invention show IC_{50} values in the range 10-1000 nM. The NK_3-antagonist activity of the compounds of the present invention is determined by their ability to inhibit senktide-induced contraction of the guinea-pig ileum (Maggi et al, **1990**, *Br. J. Pharmacol., 101*, 996-1000) and rabbit isolated iris sphincter muscle (Hall et al., **1991**, *Eur. J. Pharmacol., 199*, 9-14) and human NK_3 receptors-mediated Ca^{++} mobilization

(Mochizuki et al, **1994**, *J. Biol. Chem., 269*, 9651-9658). Guinea-pig and rabbit *in-vitro* functional assays provide for each compound tested a mean K_B value of 3-8 separate experiments, where K_B is the concentration of the individual compound required to produce a 2-fold rightward shift in the concentration-response curve of senktide. Human receptor functional assay allows the determination of the concentration of the individual compound required to reduce by 50% (IC_{50} values) the Ca^{++} mobilization induced by the agonist NKB. In this assay, the compounds of the present invention behave as antagonists.

The activity of the compounds of the present invention, as NK-2 ligands, is determined by their ability to inhibit the binding of the radiolabelled NK-2 ligands, [^{125}I]-NKA or [^{3}H]-NKA, to human NK-2 receptors (Aharony et al, **1992**, *Neuropeptide, 23*, 121-130).

The binding assays utilized allow the determination of the concentration of the individual compound required to reduce by 50% the [^{125}I]-NKA and [^{3}H]-NKA specific binding to NK-2 receptor in equilibrium conditions (IC_{50}).

Binding assays provide for each compound tested a mean IC_{50} value of 2-5 separate experiments performed in duplicate or triplicate. The most potent compounds of the present invention show IC_{50} values in the range 1-1000 nM, such as 1-100 nM. The NK-2-antagonist activity of the compounds of the present invention is determined by their ability to inhibit human NK-2 receptor-mediated Ca^{++} mobilization (Mochizuki et al, **1994**, *J. Biol. Chem., 269*, 9651-9658). Human receptor functional assay allows the determination of the concentration of the individual compound required to reduce by 50% (IC_{50} values) the Ca^{++} mobilization induced by the agonist NKA. In this assay, the compounds of the present invention behave as antagonists.

The therapeutic potential of the compounds of the present invention in treating the conditions can be assessed using rodent disease models.

As stated above, the compounds of formula (I) are also considered to be useful as diagnostic tool. Accordingly, the invention includes a compound of formula (I) for use as diagnostic tools for assessing the degree to which neurokinin-2 and neurokinin-3 receptor activity (normal, overactivity or underactivity) is implicated in a patient's symptoms. Such use comprises the use of a compound of formula (I) as an antagonist of said activity, for example including but not restricted to tachykinin agonist-induced inositol phosphate turnover or electrophysiological activation, of a cell sample obtained from a patient. Comparison of such activity in the presence or absence of a compound of formula (I), will disclose the degree of NK-2 and NK-3 receptor involvement in the mediation of agonist effects in that tissue.

Descriptions and Experimental

Nuclear magnetic resonance spectra were recorded at 400 MHz using a Bruker AC 400 spectrometer. $CDCl_3$ is deuteriochloroform, DMSO-d_6 is hexadeuteriodimethylsulfoxide, and CD_3OD is tetradeuteriomethanol. Chemical shifts are reported in parts per million (□) downfield from the internal standard tetramethylsilane. Abbreviations for NMR data are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, app = apparent, br = broad. J indicates the NMR coupling constant measured in Hertz. Continuous wave infrared (IR) spectra were recorded on a Perkin-Elmer 683 infrared spectrometer, and Fourier transform infrared (FTIR) spectra were recorded on a Nicolet Impact 400 D infrared spectrometer. IR and FTIR spectra were recorded in transmission mode, and band positions are reported in inverse wavenumbers (cm^{-1}). Mass spectra were taken on either VG 70 FE, PE Syx API III, or VG ZAB HF instruments, using fast atom bombardment (FAB) or electrospray (ES) ionization techniques. Elemental analyses were obtained using a Perkin-Elmer 240C elemental analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. All temperatures are reported in degrees Celsius.

Analtech Silica Gel GF and E. Merck Silica Gel 60 F-254 thin layer plates were used for thin layer chromatography. Both flash and gravity chromatography were carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel.

Examples

In the following synthetic examples, temperature is in degrees Centigrade (°C). Unless otherwise indicated, all of the starting materials were obtained from commercial sources. For reverse phase HPLC (unless otherwise stated), a 50 X 20 mm I. D. YMC CombiPrep ODS-A column at 20 mL/min with a 10 min gradient from 10% CH_3CN to 90% CH_3CN in H_2O was used with a 2 min hold at 90% CH_3CN in H_2O at the end of each run. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. These Examples are given to illustrate the invention, not to limit its scope. Reference is made to the claims for what is reserved to the inventors hereunder.

Example 1

2-(3,5-Difluoro-phenyl)-6-fluoro-3-{4-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-3-oxo-piperazin-1-ylmethyl}-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide

1a) {4-[4-((S)-1-Cyclohexyl-ethylcarbamoyl)-2-(3,5-difluoro-phenyl)-6-fluoro-quinolin-3-ylmethyl]-2-oxo-piperazin-1-yl}-acetic acid

A solution of 2-(3,5-difluoro-phenyl)-6-fluoro-3-(3-oxo-piperazin-1-ylmethyl)-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide (Prepared in a fashion analagous to 3-(3-oxo-piperazin-1-ylmethyl)-2-thiophen-2-yl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide – WO0244165) (400 mg, 0.76 mmol) in DMSO (3 mL) was mixed with NaH (37 mg, 60% in mineral oil, 0.91 mmol) at room temperature. The resultant mixture was stirred for 3 minutes and mixed with iodo-acetic acid ethyl ester (0.1 mL, 0.91 mmol). After stirring for 1 hr, the reaction mixture was purified via reverse phase HPLC (Gilson) to afford the title compound (75 mg, 17%); MS (ES) *m/z* 584 $(M+H)^+$.

1b) 2-(3,5-Difluoro-phenyl)- 6-fluoro-3-{4-[2-(4-methyl-piperazin-1-yl)- 2-oxo-ethyl]-3-oxo-piperazin-1-ylmethyl}-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide

A solution of {4-[4-((S)-1-cyclohexyl-ethylcarbamoyl)-2-(3,5-difluoro-phenyl)-6-fluoro-quinolin-3-ylmethyl]-2-oxo-piperazin-1-yl}-acetic acid (30 mg, 0.051 mmol) in DMF (1 mL) was mixed with 1-methyl-piperazine (1 drop, excess), HBTU (20 mg, 0.052 mmol) and diisopropyl ethyl amine (3 drops, excess). After stirring for 1 hr, the reaction mixture was purified via reverse phase HPLC to afford the title compound (10 mg, 29%); MS (ES) *m/z* 666 $(M+H)^+$.

Example 2

2-(3,5-Difluoro-phenyl)-6-fluoro-3-[3-oxo-piperidin-1-yl-ethyl)-piperazin-1-ylmethyl]-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide

The title compound was prepared from piperidine and {4-[4-((S)-1-cyclohexyl-ethylcarbamoyl)-2-(3,5-difluoro-phenyl)-6-fluoro-quinolin-3-ylmethyl]-2-oxo-piperazin-1-yl}-acetic acid with 48% yield by following the procedure of 1b; MS (ES) *m/z* 651 $(M+H)^+$.

Example 3

6-Fluoro-2-(4-fluoro-phenyl)-3-[4-(2-morpholin-4-yl-2-oxo-ethyl)-3-oxo-piperazin-1-ylmethyl]-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide

3a) {4-[4-((S)-1-Cyclohexyl-ethylcarbamoyl)-6-fluoro-2-(4-fluoro-phenyl)-quinolin-3-ylmethyl]-2-oxo-piperazin-1-yl}-acetic acid

A solution of 6-fluoro-3-(3-oxo-piperazin-1-ylmethyl)-2-(4-fluoro-phenyl)-2-yl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide (Prepared in a fashion analagous to 3-(3-oxo-piperazin-1-ylmethyl)-2-thiophen-2-yl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide – WO0244165) (80 mg, 0.168 mmol) in DMF (0.5 mL) was mixed with NaH (12.1 mg, 60% in mineral oil, 0.504 mmol) at room temperature. The resultant mixture was stirred for 3 minutes and mixed with bromo-acetic acid ethyl ester (0.0186 mL, 0.168 mmol). After stirring for 1 hr, the reaction mixture was purified via reverse phase HPLC (Gilson) to afford the title compound (85 mg, 90%); MS (ES) *m/z* 565 $(M+H)^+$.

3b) 6-Fluoro-2-(4-fluoro-phenyl)-3-[4-(2-morpholin-4-yl-2-oxo-ethyl)-3-oxo-piperazin-1-ylmethyl]-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide

A solution of {4-[4-((S)-1-cyclohexyl-ethylcarbamoyl)-6-fluoro-2-(4-fluoro-phenyl)-2-yl-quinolin-3-ylmethyl]-2-oxo-piperazin-1-yl}-acetic acid (23 mg, 0.0407 mmol) in DMF (0.5 mL) was mixed with morpholine (0.0036 mL, 0.0407 mmol), HBTU (15.4 mg, 0.0407 mmol) and 4-methyl-morpholine (0.0089 mL, 0.0814 mmol). After stirring for 1 hr, the reaction mixture was purified via reverse phase HPLC to afford the title compound (14 mg, 54%); MS (ES) *m/z* 634 $(M+H)^+$; ^{1}H-NMR($CDCl_3$) δ 1.18 (m, 6H), 1.30 (d, J = 6.7 Hz, 3H), 1.50 (m, 1H), 1.79 (m, 4H), 2.54 (m, 2H), 3.04 (m, 2H), 3.23 (m, 2H), 3.45 (m, 2H), 3.59 (m, 2H), 3.68 (m, 4H), 3.80 (m, 2H), 4.05 (d, J = 5.8 Hz, 1H), 4.14 (d, J = 5.8 Hz, 1H), 4.24 (m, 1H), 6.95 (s, br, 1H), 7.20 (m, 2H), 7.54 (m, 3H), 7.65 (m, 1H), 8.13 (m, 1H).

Example 4

6-Fluoro-2-(4-fluoro-phenyl)-3-{4-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-3-oxo-piperazin-1-ylmethyl}-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide

The title compound was prepared from {4-[4-((S)-1-cyclohexyl-ethylcarbamoyl)-6-fluoro-2-(4-fluoro-phenyl)-2-yl-quinolin-3-ylmethyl]-2-oxo-piperazin-1-yl}-acetic acid with 60% yield by following the procedure of 3b.

MS (ES) *m/z* 647 $(M+H)^+$; ^{1}H-NMR($CDCl_3$) δ 1.18 (m, 6H), 1.30 (d, *J* = 6.7 Hz, 3H), 1.50 (m, 1H), 1.79 (m, 4H), 2.30 (s, 3H), 2.41 (m, 4H), 2.54 (m, 2H), 3.00 (m, 2H), 3.18(m, 2H), 3.44 (m, 2H), 3.59 (m, 2H), 3.80 (m, 2H), 4.04 (d, *J* = 5.8 Hz, 1H), 4.15(d, *J* = 5.8 Hz, 1H), 4.23 (m, 1H), 6.90 (m, br, 1H), 7.20 (m, 2H), 7.54 (m, 3H), 7.65 (m, 1H), 8.13 (m, 1H).

Example 5

6-Fluoro-2-(4-fluoro-phenyl)-3-[3-oxo-4-(2-oxo-2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide

The title compound was prepared from {4-[4-((S)-1-cyclohexyl-ethylcarbamoyl)-6-fluoro-2-(4-fluoro-phenyl)-2-yl-quinolin-3-ylmethyl]-2-oxo-piperazin-1-yl}-acetic acid with 58% yield by following the procedure of 3b. MS (ES) *m/z* 618 $(M+H)^+$; ^{1}H-NMR($CDCl_3$) δ 1.18 (m, 6H), 1.29 (d, *J* = 6.7 Hz, 3H), 1.50 (m, 1H), 1.84 (m, 6H), 1.97 (m, 2H), 2.54 (m, 2H), 3.04 (m, 2H), 3.27(m, 2H), 3.43 (m, 4H), 3.80 (m, 2H), 3.95 (d, *J* = 6.0 Hz, 1H), 4.08(d, *J* = 6.0 Hz, 1H), 4.23 (m, 1H), 7.10 (m, br, 1H), 7.18 (m, 2H), 7.51 (m, 3H), 7.65 (m, 1H), 8.13 (m, 1H).